

*AF* *Sub B*  
to an antidote.

35

(new) The nucleic acid of claim 1, wherein the toxic agent is targeted

#### REMARKS

The specification has been amended pursuant to 37 C.F.R. § 1.821(d) to incorporate the sequence identifiers corresponding to the Sequence Listing submitted herewith and to correct typographical errors. The above-made amendments contain no new matter.

Claims 1 to 21 and 23 to 31 were pending in the instant application. Claims 8, 9, 12, and 17 have been canceled without prejudice to Applicants' right to pursue the subject matter of the canceled claims in the instant or related patent applications. Claims 1, 3, 10, 11, 16, 18, 19, 23, 26, and 28 have been amended and new claims 33 to 35 has been added to more particularly point out and distinctly claim that which Applicants deem to be the invention. With entry of the above-made amendments, claims 1 to 7, 10, 11, 13 to 16, 18 to 21, and 23 to 35 will be pending. A courtesy copy of the pending claims, as amended, is attached hereto as Exhibit A.

Claims 1, 18, 19, 26, and 28 have been amended to recite a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences. Support is found in the specification on page 17, lines 21 to 24; page 35, lines 9 to 15; and Example 9, page 77, line 28 to page 80, line 14.

Claim 3 has been amended to correct a grammatical error.

Claim 11 has been amended to recite a toxic agent is adjacent to trans-acting ribozyme. Support is found in the specification on page 5, line 33 to page 6, line 2 and page 17, lines 16 to 17.

Claim 10 has been amended to depend from claim 7.

Claim 15 has been amended to correct a typographical error.

Claims 16 and 23 have been amended to include SEQ ID numbers.

Claim 33 has been added to recite a ribozyme cassette that comprises a 5' autocatalytically cleaving ribozyme sequence and a 3' autocatalytically cleaving ribozyme

sequence. Support is found in the specification on page 17, lines 30 to 32 and page 35, lines 11 to 15.

Claim 34 has been added to recite a ribozyme with enhanced cleavage activity. Support is found in the specification on page 17, lines 32 to 34 and page 35, lines 15 to 16.

Claim 35 has been added to recite a toxic agent is targeted to an antidote. Support is found in the specification on page 12, line 35 to page 13, line 6; page 16, lines 3 to 7; page 45, lines 26 to 28; and Example 8, page 77, lines 4 to 26.

Applicants submit that the above-made amendments are fully supported in the instant application as originally filed, and do not constitute new matter.

### CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application.

Respectfully submitted,

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Laura A. Coruzzi 30,742  
(Reg. No.)

By: Stephen K. Sullivan 43,171  
(Reg. No.)

PENNIE & EDMONDS LLP  
1155 Avenue of the Americas  
New York, New York 10036-2711  
(212) 790-9090

Enclosures

EXHIBIT A



**EXHIBIT A: PENDING CLAIMS  
AS AMENDED FEBRUARY 5, 2001**

(U.S. APPLICATION NO. 09/548,449; ATTORNEY DOCKET NO. 9175-016-999)

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1. (amended) A recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences.

2. The nucleic acid of claim 1, wherein the nucleic acid comprises more than one toxic agent.

3. (amended) The nucleic acid of claim 1, wherein the toxic agent is a toxic gene product.

4. The toxic gene product of claim 3, which is an Addiction System toxin.

5. The toxic gene product of claim 3, which is a chromosomally encoded bacterial toxin.

6. The toxic gene product of claim 3, selected from the group consisting of *ccdB*, *kid*, *perK*, *parE*, *doc*, *higB*, *chpAK*, *chpBK*, *kicB*, *hoc*, *srnB'*, *fimA*, *pmdA*, *relF*, *gef*, *kilA*, *kilB*, *kilC*, *kilE*, *traL*, *traE*, *sigB*, *hok*, *pemK*, *lysostaphin*, and *kikA*.

7. The nucleic acid of claim 1, wherein the toxic agent is an antisense RNA.

10. (amended) The nucleic acid of claim 7 wherein the antisense RNA is a *DicF1*-like antisense RNA.

11. (amended) The nucleic acid of claim 2, wherein at least one toxic

agent is adjacent to trans-acting ribozyme and at least one toxic agent is toxic gene product.

13. The nucleic acid of claim 1, wherein the toxic agent is sense RNA.

14. The nucleic acid of claim 13, wherein the sense RNA is targeted to an essential antisense molecule.

15. (amended) The nucleic acid of claim 1, wherein the promoter is selected from the group consisting of a bacterial-specific promoter, a viral-specific promoter, a liver-specific promoter, a prostate-specific promoter, an epidermal-cell specific promoter, an ileum-specific promoter, a breast-specific, and a smooth muscle-specific promoter.

16. (amended) The nucleic acid of claim 1, wherein the pathogen-specific promoter is selected from the group consisting of an *anr* promoter (SEQ ID NO:3), a *ProC* promoter (SEQ ID NO:4), a *hla* promoter, a *SrcB* promoter and a *TSST-1* promoter (SEQ ID NO:6).

18. (amended) A vector comprising a recombinant nucleic acid encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences.

19. (amended) A modified virion comprising a recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences.

20. The virion of claim 19 which is a bacteriophage.

21. The bacteriophage of claim 20 which is a P1 bacteriophage.

23. (amended) The bacteriophage of claim 20 which further comprises a mutated *pac* site (SEQ ID NO:8) or a mutated *pacABC* gene.

24. The virion of claim 19, wherein the virion has a reduced ability to transfer DNA originating from the virus, and wherein the virion is capable of transferring the recombinant nucleic acid.

25. The virion of claim 19, wherein the nucleic acid encodes a toxic agent selected from the group consisting of *ccdB*, *kid*, *perK*, *parE*, *doc*, *higB*, *chpAK*, *chpBK*, *kicB*, *hoc*, *srnB'*, *flmA*, *pmdA*, *relF*, *gef*, *kilA*, *kilB*, *kilC*, *kilE*, *traL*, *traE*, *sigB*, *hok*, *pemK*, *lysostaphin*, and *kikA*.

26. (amended) A method of inhibiting replication of a pathogen in a subject, comprising administering to said subject a recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences.

27. The method of claim 26, wherein the pathogen is a bacteria.

28. (amended) A method of inhibiting replication of a pathogen in a subject, comprising administering to said subject a modified virion comprising a recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences.

29. The method of claim 28, wherein the virion is a bacteriophage.

30. The method of claim 27, wherein the pathogen is bacteria.

31. A pharmaceutical composition comprising the modified virion of claim 19, and a pharmaceutically acceptable carrier.

33. (new) The nucleic acid of claim 1, wherein the ribozyme cassette comprises a 5' autocatalytically cleaving ribozyme sequence and a 3' autocatalytically cleaving ribozyme sequence.

34. (new) The nucleic acid of claim 1, wherein one or more autocatalytically cleaving ribozymes has enhanced cleavage activity.

35. (new) The nucleic acid of claim 1, wherein the toxic agent is targeted to an antidote.